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Beta-substituted furans

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NOTE TO USERS

BETA-SUBSTITUTED FURANS

BY

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TABLE OF CONTENTS

INTRODUCTION

The chemistry of β-substituted furans is a subject which has come into prominence only within recent years. A search of the literature reveals the fact that although a variety of such compounds has been prepared, their investigation for the most part has ceased rather abruptly at this point. Indeed, in many cases the structure of these compounds has been left undetermined or an erroneous one has been assigned. In some instances substitution and degradation reactions were carried out, but the resulting products were frequently unidentified.

Such a state of progress is understandable in view of the paucity of reference compounds which were available to the earlier investigators. In addition to this they were seriously handicapped by their lack of technique in handling the more sensitive furan derivatives the properties of which are sharply contrasted to their benzene analogs. Furthermore, such valuable working tools as preferential decarboxylation, oxidation, mercuration etc., were undeveloped.

Another factor responsible for the delay in the investigation of β-substituted furans lies in the fact that they are less readily accessible than α-substituted furans. It is significant, in this connection, that apparently only one β-substituted furan is now known to occur naturally. As will be more thoroughly reviewed in the sequel, there are two general methods for the synthesis of β-substituted furans. One method involves

substitution of di-α-substituted furan derivatives which by necessity allocates the entering group to a β-position. The other, which is the more fruitful method of approach especially with regard to the simpler β-substituted furans, depends upon ring closure of certain types of reactive aliphatic derivatives.

Within the last five years the chemistry of the furan series has advanced to the point where it can no longer be treated as a subject of textbook interest only. It has become a promising field for industrial development and must be established firmly on a scientific basis. Extensive studies on constitution and orientation have become necessary in order to gain this end. In this connection mono- and di-β-substituted furan derivatives are important, since they furnish a convenient means of studying the unhampered orienting forces in nuclear substitution reactions. The resulting substitution products may be readily degraded to known reference compounds, and this has made possible the formulation of a set of rules of orientation.

METHODS OF SYNTHESIS OF β-SUBSTITUTED FURANS

As mentioned in the introduction there are two general methods for synthesizing β-substituted furans. Since the literature on this subject is quite widely scattered over a period of years, a brief summary is presented with the end in view that it may be of assistance to those who are interested in such derivatives.

I. Substitution of α-Substituted Furans

Substitution reactions so far effected with α-substituted furans may be classified as follows:

1. Nitration
2. Halogenation
3. Sulfonation
4. Mercuration
5. Friedel and Crafts' Reaction

Nitration

Under the heading of nitration we find that the range of applicability as a method of synthesis is rather limited. Only four reactions have been described in which a nitro group has been introduced into the β-position. This scarcity of successful β-nitrations seems rather unusual at first glance, but upon closer examination it becomes apparent that such results are inevitable. In light of our present knowledge it may be stated with some confidence that β-nitration is limited to di-α-substituted furans in which either one or both substituent groups

TABLE I

Source	Nitrating Agent	Product	Worker	Reference
Ethyl 5-methyl-2-furoate	Fuming nitric and $(CH_3CO)_2O$	Ethyl 5-methyl-4(?)-nitro-2-furoate	(1) Rinkes	Rec. trav. chim., 49, 1118 (1930)
Ethyl 5-acetamino-2-furoate	Fuming nitric and $(CH_3CO)_2O$	Ethyl 4(?)-nitro 5-acetamino-2-furoate	(2) Gilman and Wright	Ia. State Coll. J. Sci. 5, 85 (1931)
2,5-Dimethyl-furan	Fuming nitric and $(CH_3CO)_2O$	2,5-Dimethyl-3-nitrofuran	(3) Gilman and Burtner	Rec. trav. chim., 51, 667 (1932)
Ethyl 2,5-dimethyl-3-furoate	Fuming nitric and $(CH_3CO)_2O$	Ethyl 2,5-dimethyl-4-nitro-3-furoate		

are of a positive nature. This fact automatically excludes the great majority of the more stable di-α-substituted furans, i.e. those containing two negative groups, leaving only a narrow range of compounds some of which are obviously too unstable to withstand the experimental conditions. Another factor, which may be of primary significance, involves the relative energy requirements for α- and β-substitution reactions. Reactions

in general follow the course of least resistance. Therefore, since α-substitution where possible is strictly preferential to β-substitution, it seems logical to conclude that substitution of the former type requires less energy. If this be true, then β-nitration would require the greater amount of energy, perhaps beyond that tolerated by present conditions of nitration. Either there is no reaction or one of the reacting materials breaks down into irreversible fragments. If there is any merit in these suppositions, then it is not surprising that only a few successful β-nitrations have been effected.

Halogenation

The synthesis of β-halogenofurans has been somewhat more successful than the corresponding nitro compounds. It is true that the examples of direct halogenation in which only one halogen atom has been introduced are few. However, the preparation of polyhalogeno derivatives and their degradation to mono- and di-β-halogen substituted furans have been quite successful. Hill and his co-workers starting with α-substituted furan derivatives have prepared and studied no less than eleven compounds of this type. Another method which has been used with success involves the introduction of a halogen in the β-position by replacement of a chloromercuri group. Thus we have at our disposal a variety of β-halogenfurans containing readily removable α-substituent groups thereby affording a source of the simpler β-halogen derivatives. Although the structures of

several of the compounds described in the accompanying table are as yet undetermined, it appears certain that concerted studies on orientation will reveal their constitution.

TABLE II

Source	Halogenating Agent	Product	Worker	Reference
2,5-Dimethyl-3-furoic acid	Br_2	2,5-Dimethyl 4-bromo-3-furoic acid	(3) Gilman and Burtner	Rec. trav. chim., 51, 667 (1932)
2,5-Dimethyl-3-chloromercurifuran	KI and I_2	2,5-Dimethyl-3-iodofuran	(4) Gilman, Burtner and Wright	J. Am. Chem. Soc. 54, 1696 (1932) This thesis, page 33
2,5-Dimethyl-3-chloromercurifuran	KBr and Br_2	2,5-Dimethyl-5-bromofuran	(5) Gilman and Burtner	This thesis, page 34
Tetrachloromercurifuran	KI and I_2	Tetraiodofuran	(6) Ciusa and Grillio	Gazz. chim. ital., 57, 523 (1927)
Tetraiodofuran	Dehalogenation by Al-Hg	3-Iodofuran	(7) Gilman and Wright	J. Am. Chem. Soc., 55, 3302 (1933)
3-Chloromercurifuran	KI and I_2	3-Iodofuran		
Ethyl-5-methyl-2-furoate	Br_2	5-Methyl-?-bromo-2-furoic acid	(8) Hill and Jennings	Am. Chem. J., 15, 174 (1893)
Ethyl-5-methyl-2-furoate	Cl_2	5-Methyl-?-chloro-2-furoic acid		

TABLE II (Cont'd.)

Source	Halogenating Agent	Product	Worker	Reference
Ethyl 2-furoate	Cl_2	Trichloro-2-furoic acid	(9) Hill and Jackson	Proc. Am. Acad., 24, 320 (1888)
Ethyl tetrachloro-2-furoate	Dehalogenation by alc. KOH	3,4-Dichloro-2-furoic acid		
Ethyl tetrachloro-2-furoate	Pyrolysis	4,5-Dichloro-2-furoic acid		
Ethyl tetrachloro-2-furoate	Pyrolysis	5,5-Dichloro-2-furoic acid		
4,5-Dichloro-2-furoic acid	Dehalogenation by zinc	4-Chloro-2-furoic acid		
3,4-Dichloro-2-furoic acid	Dehalogenation by Na-Hg	4-Chloro-2-furoic acid		
Ethyl 2-furoate	Br_2	Tribromo-2-furoic acid	(10) Hill and Sanger	Proc. Am. Acad., 21, 180 (1884)
Ethyl 2-furoate	Br_2	4,5-Dibromo-2-furoic acid		
4,5-Dibromo-2-furoic acid	Dehalogenation by zinc	4-Bromo-2-furoic acid		
Diethyl dehydromucate	Cl_2	3,4-Dichloro-dehydromucic acid	(11) Gilman and Vanderwal	Rec. trav. chim., 52, 267 (1933)
3,4-Dichloro-dehydromucic acid	Decarboxylation	3,4-Dichloro-2-furoic acid		

TABLE II (Cont'd.)

Source	Halogenating Agent	Product	Worker	Reference
4-Chloro-2-furoic acid	Decarboxylation	3-Chlorofuran	(12) Shepard, Winslow and Johnson	J. Am. Chem. Soc., 52, 2083 (1930)
4-Bromo-2-furoic acid	Decarboxylation	3-Bromofuran		

Sulfonation

A search of the literature reveals the fact that only three reactions have been effected which resulted in the introduction of a sulfonic group in the β-position. Here, as in the case of β-nitration, we may attribute the failure of many attempted reactions to the restrictions imposed by experimental conditions. Either the starting material is inert due to the presence of negative groups as with diethyl dehydromucate or else it is highly sensitive toward mineral acids as with 2,5-dimethylfuran. This restricts the field of sulfonation by our present methods to a relatively small number of compounds, which are capable of surviving contact with mineral acids and yet active enough to permit substitution. The following reactions have been described, although the structures of none of the resulting sulfonic acids have been absolutely determined.

TABLE III

Source	Sulfonating Agent	Product	Worker	Reference
5-chloro-2-furoic acid	Fuming sulfuric	5-Chloro-?-sulfo-2-furoic acid	(8) Hill and Jennings	Am. Chem. J., 10, 418 (1888)
5-Bromo-2-furoic acid	Fuming sulfuric	5-Bromo-?-sulfo-2-furoic acid		
5-Methyl-2-furoic acid	Fuming sulfuric	5-Methyl-?-sulfo-2-furoic acid		

Mercuration

This new tool in furan chemistry has been quite successful in the few cases where it has been applied to the problem of β-substitution.

TABLE IV

Source	Mercurating Agent	Product	Worker	Reference
Furan	Mercuric acetate	Tetraacetoxymerfurifuran + Triacetoxymercurifuran	(6) Ciusa and Grillio	Gazz. chim. ital., 57, 323 (1927)
Acetoxymercury furoate	Rearrangement	3-Acetoxymercurifuran	(7) Gilman and Wright	J. Am. Chem. Soc., 55, 3302 (1933)
2,5-Dimethylfuran	Mercuric chloride	2,5-Dimethyl-3-chloromercurifuran	(4) Gilman, Burtner and Wright	J. Am. Chem. Soc., 54, 1696 (1932)

The results of Gilman and Wright as cited in the accompanying table are unique inasmuch as they started with a mono-α-substituted furan and obtained 3-acetoxymercurifuran as their final product. This is the only known instance in which a mono-β-substituted furan has been directly prepared from a mono-α-substituted derivative.

Although only three β-mercurations have been reported, this is by no means indicative that such reactions are generally unsuccessful. On the contrary mercuration is one of the few reactions which is applicable to a wide variety of compounds either negatively or positively substituted. Mercuration does not suffer the limitations imposed upon those reactions which involve the use of mineral acids. Hence, it is admirably adapted to the more sensitive types such as 2,5-dimethyl furan, which undergoes mercuration with extraordinary ease in satisfactory yield. In the case of the more negatively substituted furans it appears altogether probable that equally gratifying results may be obtained merely by intensifying experimental conditions. These advantages, supplemented by the increasing number of replacement reactions of the chloromercuri group, designate mercuration as a fertile field in the problem of β-substitution.

Friedel and Crafts' Reaction

Although numerous Friedel and Crafts' reactions effecting α-substitution have been reported, only two reactions of this

type involving β-substitution are known. As yet this method of substitution in the β-position has not been thoroughly investigated and may produce valuable results as our knowledge of experimental procedure is augmented. It might also be mentioned in this connection that the related Gattermann-Koch reaction for the direct introduction of an aldehyde group has received but little attention with regard to β-substitution.[13]

TABLE V

Source	Reagents used	Product	Worker	Reference
2,5-Dimethyl-furan	$(CH_3CO)_2O$ and $AlCl_3$	2,5-Dimethyl-3-acetyl-furan	(3) Gilman and Burtner	Loc. cit.
Methyl 5-methyl 2-furoate	$(CH_3CO)_2O$ and $SnCl_4$	Methyl 5-methyl-4-acetyl-2-furoate	(14) Gilman and Calloway	J. Am. Chem. Soc., 56, 0000 (1934)

II. Ring Closure Reactions Starting with Aliphatic Derivatives.

The preparation of β-substituted furans by ring closure is by far the most fruitful method of synthesis, since only in this manner can many of the simpler types of mono- and di-β-substituted derivatives be prepared. In particular, those furans containing in the β-positions such groups as carboxyl, alkyl, aryl and hydroxyl, which may be indirectly synthesized only with difficulty by substitution of α-substituted furans,

13. Reichstein, Helv. chim. acta., 13, 345 (1930).

may be prepared with ease directly by ring closure methods.

Ring closure reactions may be divided into four groups as follows:

A. Benary Synthesis

B. Diketone Synthesis

C. Coumalic Acid Synthesis

D. Miscellaneous

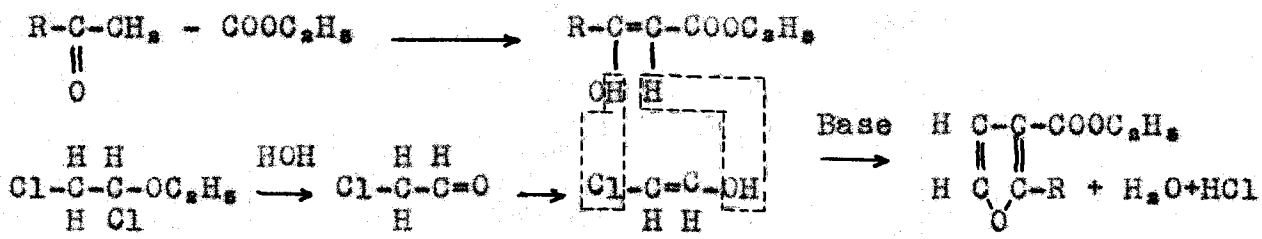
It will be noted from their mechanisms that, although a variety of starting materials may be used, the same general course of reaction is followed by many of these transformations. Enolization followed by the loss of water of HX in the presence of a condensing agent is typical.

A. Benary Synthesis

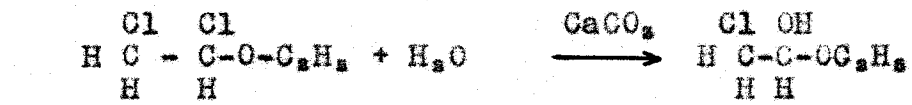
The Benary synthesis[15], which involves the condensation of acylacetic esters with reactive halogeno aliphatic ethers, aldehydes or ketones in the presence of a base, yields 2-alkyl or aryl-3-furoic acids. Compounds of this type are of particular significance. 2-methyl-3-furoic acid upon oxidation by means of bromine yields 2,3- furandicarboxylic acid, an important reference compound in orientation studies. The 2-furyl- and 2-phenyl furoic acids are admirably suited as starting materials for the preparation of compounds which should serve to throw light on the stereo or spatial configuration of furan

15. Benary, Ber., 44, 496 (1911). See also Plancher and Albini, Atti. acad. Lincei, /5/ 13, I, 39 (1904); Natterer, M, 5, 491 (1884)

compounds after the related diphenyl type of isomerism. On the basis of this well established type of stereoisomerism which found its fullest confirmation in the resolution of racemates, it appears altogether reasonable to expect that related optically active furan compounds will be obtained with the introduction of proper substituents in the critical positions. The most logical reaction mechanism which may be gleaned from the literature cited is shown as follows:



This mechanism appears plausible for two reasons. First, α,β-dichloroethyl ether reacts in the presence of water in the following manner[16]:



The calcium carbonate merely serves as a buffer to remove the hydrogen chloride from solution. If the reaction is unbuffered, the hemi-acetal readily breaks down to the corresponding aldehyde. Second, Plancher and Albini[15] as well as Natterer[15] showed that chloroacetaldehyde and ethyl acetoacetate react in the presence

16. Fritsch and Schumacher, Ann., 279, 301 (1894).

of ammonia in ether solution to form ethyl 2-methyl -3-furoate. If dichloroethyl ether is used in this synthesis, obviously the reaction must be carried out in aqueous solution. When the halogenated aldehydes or ketones are employed, anhydrous conditions must be maintained using ether as a solvent and gaseous ammonia as the condensing agent. The following β-substituted furans have been prepared by this method of synthesis:

TABLE VI

Source	Reagents Used	Product	Worker	Reference
Ethyl aceto-acetate	Dichloro-ethyl ether and NH_4OH	Ethyl 2-methyl-3-furoate	(15) Benary	Ber., 44, 493 (1911)
Ethyl aceto-acetate	Dichloro-ethyl ether and NaOH	Ethyl 2-methyl-3-furoate	(17) Gilman, Burtner and Smith	Rec. trav. chim., 51, 407, (1932)
Ethyl 2-furoyl-acetate	Dichloro-ethyl ether and NH_4OH	Ethyl 2,2'-furyl-3-furoate	(18) Kondo and Suzuki	J. Pharm. Soc. Japan, 554, 501 (1927) / C.A., 21, 3362 (1927) /
Ethyl 2-furoyl-acetate	Dichloro ethyl ether and NaOH	Ethyl 2,2'-furyl-3-furoate	(19) Gilman and Burtner	Ia. State Coll. J. Sci., 5, 189 (1931)
Ethyl benzoyl-acetate	Dichloro-ethyl ether and NH_4OH	Ethyl 2-phenyl-3-furoate	(20) Fujita	J. Pharm. Soc. Japan, 519, 450 (1925) / C.A., 20, 759 (1926) /

TABLE VI (Cont'd.)

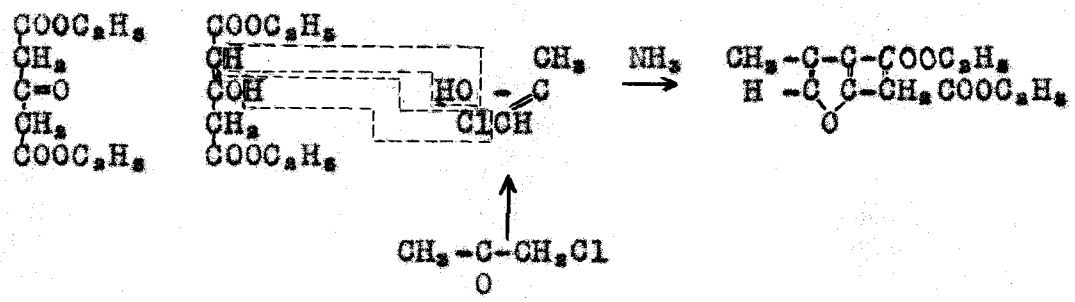
Source	Reagents Used	Product	Worker	Reference
Ethyl benzoyl-acetate	Dichloro-ethyl ether and NaOH	Ethyl 2-phenyl-3-furoate	(19) Gilman and Burtner	Loc. cit.
Ethyl aceto-acetate	Chloro-acetaldehyde and NH_3	Ethyl 2-methyl-3-furoate	(15) Plancher and Albini; Natterer	Loc. cit.
Ethyl aceto-acetate	Chloro-acetone and NH_3	Ethyl 2,4-dimethyl-3-furoate	(15) Plancher and Albini	Loc. cit.
Isopropyl aceto-acetate	Dichloro-ethyl ether and NaOH	Ethyl 2-isopropyl-3-furoate	(21) Reichstein Zschokke, Gehring and Rona	Helv. chim. acta., 15, 1118 (1932)

It is worthy of mention at this point that in those syntheses where dichloroethyl ether is used with aqueous ammonia as a condensing agent a considerable portion of the yield consists of the corresponding pyrrol derivative. In some cases the separation of the furan from the pyrrol derivative is inefficient and tedious. To circumvent this difficulty aqueous alkali was substituted as the condensing agent in which instance no pyrrol compounds are formed. Recently, Johnson[22] has shown that aqueous pyridine may be used in the preparation of ethyl 2-methyl-3-furoate. By this method he obtained yields of 60-65%, which is considerably higher than any hitherto reported. No

22. Private communication from Dr. J. R. Johnson to G. F. Wright.

pyrrol derivative was formed in this case. Whether aqueous pyridine may be generally applied to the preparation of related types of compounds is yet to be determined.

A related method of ring closure, which by virtue of its mechanism is essentially a Benary synthesis, was devised by Feist[23] and improved by Reichstein[24]. Ethyl acetonedicarboxylate and chloracetone are condensed under anhydrous conditions with gaseous ammonia to form ethyl-4-methyl-3-carboethoxy-2-furylacetate plus a small amount of the corresponding pyrrol derivative. The mechanism follows:



This synthesis is important, since the substituted ethyl furylacetate thus formed serves as the starting material for the preparation of a number of the simpler β-substituted furans[24]. It would be of interest to determine whether mono-α-halogenoketones of the general type

$$R - \overset{O}{\overset{\|}{C}}-CH_2Cl \quad R'$$

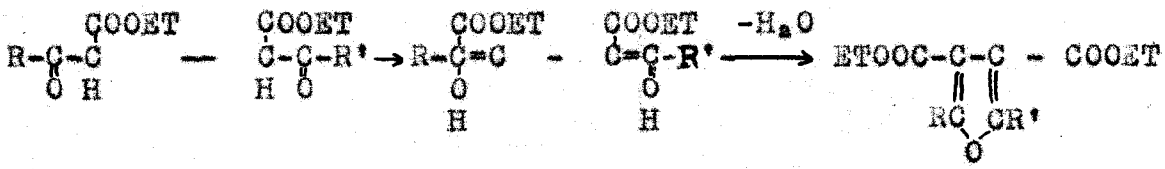
may be substituted for chloracetone in this reaction. If

23. Feist, Ber., 35, 1539 (1902).
24. Reichstein and Zschokke, Helv. chim. acta., 14, 1270 (1931).

this proves to be possible, the utility of this method of synthesis would be extended considerably. Reichstein[25] recently reported the reaction between ethyl acetonedicarboxylate and -chloroethyl methyl ketone in the presence of gaseous ammonia to yield ethyl 4,5-dimethyl-3-carboethoxy-2-furylacetate. He also showed that -chloromethyl ethyl ketone reacts in a similar manner with the formation of ethyl 4-ethyl-3-carboethoxy-2-furylacetate[26].

B. Diketone Synthesis

This method of ring closure synthesis involves the elimination of water from -diketones by means of such dehydrating agents as sulfuric acid, hydrogen chloride, zinc chloride, etc. according to the mechanism



The R groups may be alkyl, aryl or mixed groups. In some cases the diketone contains only one carboethoxyl group in which instance the corresponding -monobasic acid derivative is formed.

Among the more common starting materials are the diketosuccinic acid derivatives. The sodium salts of acylacetic esters are condensed by means of bromine or iodine to form the desired diketone, from which water is then eliminated yielding a tetra-

25. Reichstein and Grussner, Helv. chim. acta., 16, 28 (1933).
26. Reichstein and Grussner, Helv. chim. acta., 16, 6 (1933).

or in some cases a trisubstituted furan depending upon the nature of the diketone and the method of dehydration employed.

TABLE VII

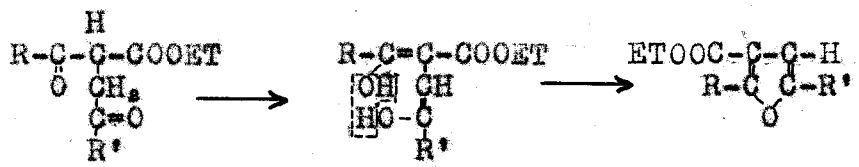
Source	Dehydrating Agent	Product	Worker	Reference
Diaceto-succinic ester	Conc. sulfuric	Diethyl 2,5-dimethyl-3,4-furandicarboxylate	(27) Knorr	Ber., 17, 2865 (1884)
Diaceto-succinic ester	Dil. sulfuric	2,5-dimethyl-3,4-furandicarboxylic acid and Ethyl 2,5-dimethyl-3-furoate	(28) Harrow	Ann., 201, 145 (1880)
Dibenzoyl-succinic ester	Conc. sulfuric	Diethyl 2,5-diphenyl 3,4-furandicarboxylate	(29 Perkin and Baeyer	Ber., 17, 59 (1884)
Dioxal-succinic ester	Dil. sulfuric	Triethyl 2,3,4-furantricarboxylate	(30) Sutter (a)	Ann., 499, 47 (1932)
Dioxal-succinic ester	Conc. sulfuric	Tetraethyl furantetracarboxylate	(31) Reichstein Grussner Schindler and Hardmeier	Helv. chim. acta., 16, 276 (1933)
-Acetyl--propionyl-propionic acid	Conc. sulfuric	Ethyl 5-ethyl-2-methyl-3-furoate	(26) Reichstein and Grussner	Loc. cit.

(a) Sutter believed that his product was the 2,3,5-furantricarboxylic acid derivative. Later Reichstein / Helv. chim. acta., 16, 555 (1933) / proved it to be the 2,3,4-derivative.

TABLE VII (Cont'd.)

Source	Dehydrating Agent	Product	Worker	Reference
Ethyl diacetobutyrate	Conc. sulfuric	2,4,5-Trimethyl-3-furoic acid	(52) Reichstein, Zschokke and Syz	Helv. chim. acta., 15, 1112 (1932)

A related type of diketone synthesis depends on the elimination of water from coupling products of sodium acylacetic esters and halogenoaldehydes and ketones.



Obviously, when R' is a hydrogen atom, the resulting product will be a 2-alkyl or aryl-3-furoic acid derivative. However, all attempts to effect a condensation in which R is a hydrogen atom have failed, probably due to the peculiarities of formylacetic ester [33].

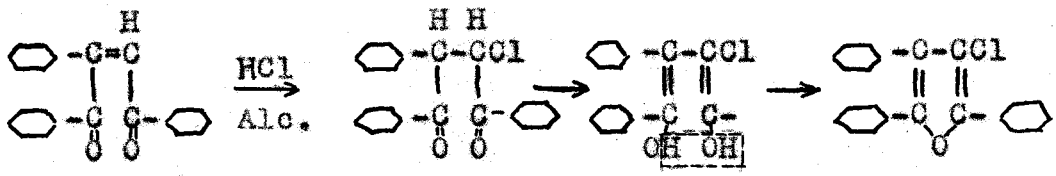
The following ring closure reactions of this type have been described:

33. Pechmann, Ber., 25, 1040 (1892).

TABLE VIII

Source	Dehydrating Agent	Product	Worker	Reference
Ethyl acetonyl-aceto-acetate	Fuming HCl	Ethyl 2,5-dimethyl-3-furoate	(34) Weltner	Ber., 17, 66 (1884)
Ethyl phenacyl-aceto-acetate	Fuming HCl	Ethyl 2-methyl-5-phenyl-3-furoate	(35) Paal	Ber., 17, 2762 (1884)
Ethyl formyl-methyl-aceto-acetate	Fuming HCl	Ethyl 2-methyl-3-furoate	(36) Gilman and Burtner	This thesis, page 46
Ethyl phenacyl-benzoyl-acetate	Alcoholic HCl	Ethyl 2,5-diphenyl-3-furoate	(37) Kapf and Paal	Ber., 21, 1491 (1888)

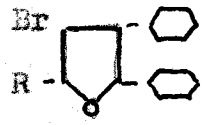
A third type of γ-diketone synthesis depends upon the elimination of water from diacylstyrene and stilbene derivatives as follows:



In this manner Japp and his co-workers[38] have prepared 2,3,5-diphenyl-4-chlorofuran, tetraphenylfuran[38], 2,3-diphenyl-4-tertiary butyl furan[39], and 2,3-diphenyl-4-acetyl-5-tertiary-

38. Japp and Klingemann, J. Chem. Soc., 57, 662 (1884).
39. Japp and Maitland, J. Chem. Soc., 85, 1499 (1904).

butyl furan[39]. Allen and Rosener[40] treated a number of substituted acylstyrenes with hydrogen bromide to obtain compounds of the type



in which R may be phenyl, p-tolyl, o-xylyl, p-anisyl, p-chlorophenyl, 4-chloro-3-methylphenyl and p-bromophenyl. Allen and Bridgess[41] heated γ-bromo-γ-nitro-γ-phenylbutyrophenone with acetic acid obtaining 2,5-diphenyl-3-bromofuran and 2,5-diphenyl-3,4-dibromofuran. Allen and Hermann[42] also prepared 2,3,5-triphenyl-3-bromofuran by treating desylacetophenone with bromine. At the Spring meeting of the American Chemical Society (1933) Lutz and Taylor reported the formation of 2,5-diphenyl-3,4-dimethylfuran from the reduction and dehydration of di /trimethylbenzoyl/-dimethyl-ethylene.

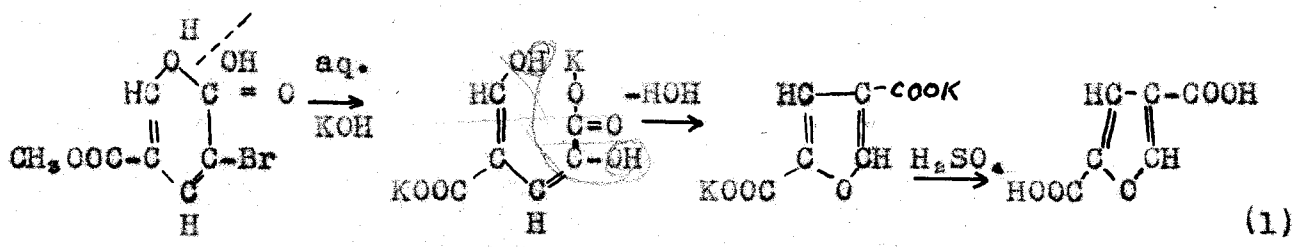
It must be noted that, although the structures of these polyphenylfurans are probably correct, their furanic structures remain to be established.

C. Coumalic Acid Synthesis

This third general class of ring closure reactions for the preparation of β-substituted furans is rather narrow in scope as

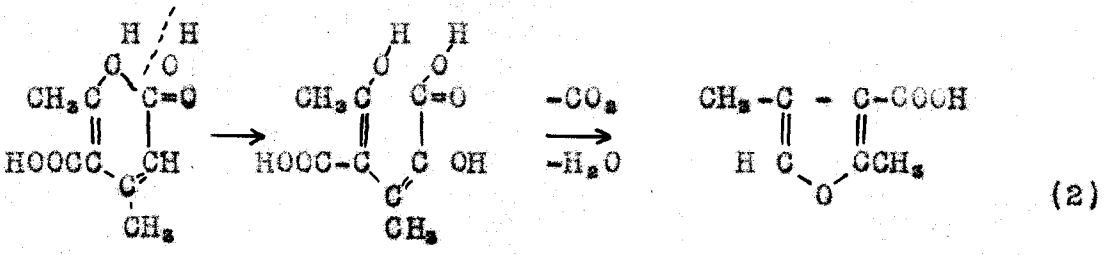
40. Allen and Rosener, J. Am. Chem. Soc., 49, 2110 (1927).
41. Allen and Bridgess, J. Am. Chem. Soc., 51, 2151 (1929).
42. Allen and Herrmann, J. Am. Chem. Soc., 51, 3591 (1929).

yet, only two cases having been reported. However, this synthesis is of primary importance, since it probably serves as the most suitable approach in the preparation of 3-furoic acid. Starting with methylbromocoumalate Feist[43] obtained 2,4-furandicarboxylic acid as follows:



(1)

He also treated dimethylcoumalic acid with aqueous bromine to obtain 2,4-dimethyl-3-furoic acid[44].



(2)

It is evident that the presence of the methyl groups in the dimethylcoumalic acid effects the C-H linkage of the α-carbon atom, undoubtedly rendering it more labile. In any event the course of ring scission and subsequent closure appears to be different in these two reactions. When dimethylbromocoumalate is treated with aqueous alkali, a reaction occurs but the

43. Feist, Ber., 34, 1993 (1901).
44. Feist, Ber., 26, 759 (1893).

expected 2,4-dimethyl-3,5-furandicarboxylic acid is not formed. By analogy with reaction (2) coumalic acid on treatment with aqueous bromine should yield 3-furoic acid. However, repeated attempts over a wide range of temperature have been unsuccessful[45]. In all probability a careful investigation of ring scission in the pyrone series would shed light on this situation and possibly extend the utility of this method of synthesis.

D. Miscellaneous Ring Closure Reactions

Under this caption there appears a variety of transformations resulting in the formation of β -substituted furans, which cannot as yet be classified as general reactions. In several of the cases cited in the accompanying table the reaction mechanisms are not clearly understood, and reasonable doubt may be raised as to whether these compounds contain the furan nucleus.

45. This thesis, page 44.

TABLE IX

Source	Treatment	Product	Worker	Reference
Benzil and diethyl diglycolate	Condensation by $NaOC_2H_5$	Diethyl 3,4-diphenyl-2,5-furandicarboxylate +	(46) Hinsberg	Ber., 45, 2414 (1912)
Dimethyl oxalate and diethyl diglycolate	Condensation by $NaOC_2H_5$	Diethyl 3,4-dimethoxy-2,5-furandicarboxylate +		
Ethyl acetoacetate and sodium succinate	Condensation by $(CH_3CO)_2O$	2-methyl-3-carboethoxy-5-furylacetic acid	(47) Fittig	Ber., 18 2526 (1885) Ann., 250, 166 (1888)
Ethyl acetoacetate and sodium methylsuccinate	Dehydration by $(CH_3CO)_2O$	2-methyl-3-carboethoxy-5-furylpropionic acid	(a)(48) Fittig and Dietzel	Ann., 250, 197 (1888)
Pyruvic acid	Barium hydroxide	2,5-dimethyl-3-furoic acid	(49) Bottinger	Ann., 172, 242 (1872)
Tartaric acid	Dry distillation	2,5-dimethyl-3-furoic acid	(50) Wislicenus and Stadnicky	Ann., 146, 306 (1868)
Dypnone	Dehydrogenation by means of nitrobenzene	2,4-diphenylfuran +	(51) Engler and Dengler	Ber., 26, 1444 (1893)
Methyl 5-ketorhamonate	Hydrogen chloride	Methyl 5-methyl-3-methoxy-2-furoate +	(52) Votaček and Malachta	Collection Czechoslov. Chem. Communications, 1, 449 (1929)

\+ Furan structure not proven.

a Fittig and Dietzel supposed this compound to be ethyl 2,3,4-trimethyl-5-furoate. This was shown to be erroneous by Reichstein and his co-workers[26].

Hinsberg's synthesis of the dihydroxyfuran derivative is worthy of note because of its relationship to ascorbic acid.

EXPERIMENTAL PART

I. Study of 2,5-Dimethylfuran and its Derivatives[+]

At the time when this study was initiated there appeared to be some doubt as to whether 2,5-dimethylfuran was a true furan derivative. It was known that this compound was extremely sensitive toward mineral acids and alkalies and that it underwent hydrolysis with uncommon ease to form acetonylacetone. Since these properties prevented the degradation of dimethylfuran to a known furan derivative, it was necessary to determine its structure by synthesis from starting materials of known furan origin.

Synthesis of 2,5-Dimethylfuran from Methylfurfural

Although Reichstein[13] had already effected this reaction, it was necessary to check it in order to obtain a sample for comparative purposes. The hydrazone of the aldehyde was prepared in the customary manner from 12.6 g. (0.11 mole) of methylfurfural and 11.0 g. (0.22 mole) of hydrazine hydrate. Upon treatment with solid potassium hydroxide the dimethylfuran distilled over at 94°, which was then dried over calcium chloride and redistilled, collecting the product boiling at 91-92°. The yield was 10 g. or 94.4% of the theoretical.

Mercuration of 2,5-Dimethylfuran

A solution of 10 g. (0.104 mole) of the above dimethylfuran in 50 cc. of ethanol was added to the mercurating solution

+ For related studies see Gilman and Burtner (3).

prepared from 27.1 g. (0.1 mole) of mercuric chloride, 16.4 g. (0.2 mole) of anhydrous sodium acetate and 500 cc. of water. Precipitation began within one minute and, after stirring for two days, the reaction was complete. The crude product, evidently a complex of the type described by Gilman and Wright[7], was filtered out and refluxed with 200 cc. of ethanol for two hours. The chilled filtrate yielded 12 g. (33%) of a pale yellow crystalline solid melting at 139-140°:

Anal. Calc'd. for C_6H_7OClHg: Hg, 60.6. Found: Hg, 60.14

A mixed melting point with the mercurial prepared in the same manner from the commercial product showed no depression.

Synthesis of 2,5-Dimethylfuran from 2-Methylfuran

2-Methyl-5-furylmagnesium iodide was prepared from 2-methylfuran through the mercurial according to the directions of Gilman and Wright[7]. 10.71 g. (0.085 mole) of dimethylsulfate dissolved in 30 cc. of absolute ether was added dropwise with stirring at laboratory temperature to a solution of 0.085 mole (determined by titration) of the organomagnesium halide under an atmosphere of nitrogen. After a gentle reflux for thirty minutes, the reaction mixture still showed a faint color test for RMgX. It was then hydrolyzed with dilute ammonium chloride and extracted with ether, and the ethereal extract washed with sodium bisulfite solution and finally dried over anhydrous sodium sulfate. By use of a 30 cm. fractionating column, the ether was carefully distilled off and the residual material

fractionated, collecting the product boiling at 85-90°. The monomercurial of this compound was identical with that prepared from the commercial dimethylfuran as well as with that obtained from the other synthetic product, as shown by mixed melting point determinations.

2,5-Dimethyl-3-Iodofuran

124 g. (0.37 mole) of 2,5-dimethyl-3-chloromercurifuran was suspended in 740 cc. of water and stirred vigorously during the slow addition of a solution of 93.9 g. (0.37 mole) of iodine and 122.8 g. (0.74 mole) of potassium iodide in 740 cc. of water. After an additional stirring for one hour, the slight excess of iodine was reduced with sulfur dioxide and the mixture steam distilled from a 12-liter balloon flask. The spicy-smelling yellow oil which collected in the distillate was removed by decantation and combined with the ethereal extract of the mother liquor. After being dried over anhydrous sodium sulfate, the ether was removed and the residual material fractionated under an atmosphere of nitrogen, collecting the portion boiling at 64-64.5°/10 mm. The yield was 31.4 g. or 38.1% of the theoretical. n_D^{20} 1.5389, d_4^{25} 1.7081.

Anal. Calc'd. for C_6H_7OI: I, 57.21. Found: I, 57.43

About 5 g. of a white crystalline solid remained in the distillation flask which after crystallization from acetone melted at 162°. This unidentified product contained mercury and was probably some R_2Hg compound carried over during steam distillation.

2,5-Dimethyl-3-Bromofuran

In a similar manner 165 g. (0.5 mole) of 2,5-dimethyl-3-chloromercurifuran in one liter of water was treated with a solution of 80 g. (0.5 mole) of bromine and 119 g. (1.0 mole) of potassium bromide in 825 cc. of water. Extraction of the steam distillate yielded but 4 g. of a pale yellow oil boiling at 54-56°/27 mm. n_D^{20} 1.4421

Anal. Calc'd. for C_6H_7OBr: Br, 45.71. Found: Br, 45.60

No color test was obtained when 2,5-dimethyl-3-bromofuran was allowed to stand for one week in ether solution with activated magnesium.

Attempted Preparation of 2,5-Dimethyl-3-Iodofuran from 2,5-Dimethyl-3-Furoic Acid

8.1 g. (0.05 mole) of sodium 2,5-dimethyl-3-furoate, 12.7 g. (0.05 mole) of iodine, 25 g. (0.15 mole) of potassium iodide and 150 g. of water were heated in a steam autoclave at approximately 150° for one hour. After cooling, the excess iodine was reduced with sulfur dioxide and the solution steam distilled with no result. The aqueous reaction mixture was filtered hot and concentrated to one half its volume. 75% of the original acid was recovered.

2,5-Dimethyl-3-Furylmagnesium Iodide

This reaction was carried out with the assistance of E. A. Zoellner. 12.1 g. (0.5 mole) of 30-80 mesh magnesium was placed in a three-necked flask with 33 cc. of ether.

Twenty drops of the halide were added with a crystal of iodine, and, since the reaction did not start, a similar portion of the halide and a small amount of activated magnesium were then added, at which point reaction set in. The remaining halide (22 g. or 0.1 mole in all) dissolved in 66 cc. of ether was added dropwise and the reaction mixture then refluxed gently for an additional thirty minutes. Titration of the filtrate showed an 18% yield of RMgX.

Carbonation at -15° yielded a small amount of a white crystalline acid melting at 135°, which was identified as 2,5-dimethyl-3-furoic acid by a mixed melting point determination. An attempt to prepare the α-naphthalide by treating the Grignard reagent with α-naphthyl isocyanate was unsuccessful.

Attempted Preparation of 2,5-Dimethyl-3-Furyllithium

5.5 g. (0.025 mole) of 2,5-dimethyl-3-iodofuran dissolved in 7.5 cc. of absolute ether was added to 0.38 g. (0.054 mole) of finely sliced lithium in 7.5 cc. of ether. After a gentle heating a reaction set in, which appeared to be complete after being stirred for one and one-half hours under reflux. The filtered solution showed a positive color test and a titration yield of 66.6%. Carbonation and treatment with α-naphthyl-isocyanate, however, did not yield the expected dimethylfuroic acid or the naphthalide. A check run showed similar results. It has since been demonstrated in this laboratory that colloidal lithium as well as other reactive metals are capable of giving

a positive color test. Whether this was the course of reaction in this case has not as yet been absolutely determined.

Attempted Direct Halogenation of 2,5-Dimethylfuran

1. Chlorination

In accordance with the directions of Fischer and Orth[53], 3.5 g. (0.036 mole) of dimethylfuran was treated in ether solution at -5° with 32 g. (0.23 mole) of sulfuryl chloride. After hydrolysis with 300 g. of ice water the ethereal layer was decanted off and washed repeatedly with water. The ethereal extract was dried over sodium sulfate and the solvent removed, leaving a small amount of unreacted dimethylfuran and a black tarry substance which was intractable.

2. Bromination

24 g. (0.25 mole) of dimethylfuran dissolved in 100 cc. of carbon disulfide was stirred at 5° during the slow addition of 80 g. (0.5 mole) of bromine. The reaction mixture became darkly colored with the addition of the first few cc. of bromine. Stirring was continued at 5° for an hour after the addition of the bromine, at which point copious evolution of hydrogen bromide occurred. The solvent was then removed under reduced pressure and the black tarry residue subjected to steam distillation. The major portion of this material immediately formed a coke-like mass, although a trace of a yellow oil was

53. Fischer and Orth, Ann., 489, 62 (1931)

observed in the steam distillate, which was removed by extraction and was shown to contain bromine. A second run, in which the reaction time was increased to two hours, yielded a similar result. Equally unsatisfactory results were obtained in an attempted bromination by means of a bromine-pyridine complex. A solution of the pyridine-bromine complex prepared from 80 g. (0.5 mole) of bromine and 39.5 g. (0.5 mole) of pyridine in carbon disulfide and chloroform was added to 24 g. (0.25 mole) of dimethylfuran in 100 cc. of chloroform. The reaction mixture was shaken for three days and then subjected to steam distillation resulting in complete decomposition.

3. Iodination

75 g. (0.35 mole) of yellow mercuric oxide and 109 g. (0.43 mole) of iodine were added alternately with constant shaking in small portions over a period of twenty minutes to a solution of 40.3 g. (0.42 mole) of dimethylfuran in 50 cc. of dry benzene contained in a 500 cc. glass-stoppered bottle immersed in an ice bath. The precipitated mercuric iodide was filtered out and washed thrice with ether. The filtrate was washed with sodium thiosulfate solution and dried, after which the solvent was removed under reduced pressure and the residual material steam distilled with complete decomposition.

2,5-Dimethyl-3-Furaldehyde

5 g. (0.031 mole) of 2,5-dimethyl-3-furoyl chloride was reduced in the usual manner with hydrogen and palladium-barium sulfate

catalyst[54]. Upon completion of the reduction, the catalyst was filtered out and the filtrate shaken with a solution of sodium bisulfite. After being washed with ether the aqueous solution of the bisulfite addition product was treated with sodium carbonate until it was distinctly alkaline and then steam distilled. Ethereal extraction of the distillate yielded 1.2 g. of the aldehyde boiling at 79°/15 mm. As expected this aldehyde gave a positive Schiff's test but no aniline acetate test. The hydrazone melted at 145° when crystallized from ethanol.

Anal. Calc'd. for $C_7H_8O_2$: C, 67.75; H, 6.45
Found: C, 67.98; H, 6.18

Oxidation of 2,5-Dimethyl-3-Nitrofuran

3-Nitrofuran has not been prepared, and it was hoped that oxidation of 2,5-dimethyl-3-nitrofuran might yield 3-nitro-2,5-furandicarboxylic acid, which upon decarboxylation would give the desired nitrofuran.

1 g. (0.007 mole) of 2,5-dimethyl-3-nitrofuran[3], 2 g. of potassium permanganate and 30 cc. of nitric acid (sp. g., 1.2) were heated in a sealed tube for eight hours at 130°. The greater portion of the material was recovered unchanged, although a small amount of a pale yellow solid melting at 158-162° was isolated from the reaction mixture. Owing to the small amount of this product available it is as yet unidentified.

54. Gilman and Burtner, J. Am. Chem. Soc., 55, 2903 (1933).

Nitration of 2,5-Dimethyl-3-Furoic Acid

The work of Rinkes[55] has shown that nitration of α-furancarboxylic acids is invariably accompanied by replacement of the carboxyl group by a nitro group. It was desired to determine whether this replacement might be effected with β-carboxylic acids. 17.8 g. (0.127 mole) of 2,5-dimethyl-3-furoic acid was added in small portions with stirring at -10° to the nitrating mixture prepared in the usual manner from 16 g. (0.254 mole) of fuming nitric acid and 46 g. of acetic anhydride. The addition of each portion of the furoic acid was accompanied by noticeable evolution of gas and a marked temperature rise. After being stirred for an additional thirty minutes, the mixture was poured into ice water, extracted several times with ether, and the ethereal extract washed with water and dried over sodium sulfate. Upon removal of solvent there remained about 8 cc. of a yellow oil which completely decomposed on vacuum distillation. Large quantities of nitric oxide were liberated, and a small amount of a white crystalline material was collected in the receiver. This material was washed out with ether and crystallized from water in the form of small white needles melting at 227°, which did not contain nitrogen.

Attempted Oxidation of Diethyl 2,5-Dimethyl-3,4-Furandicarboxylate

Following the work of Asahina[56] who has oxidized methyl

55. Rinkes, Rec. trav. chim., 52, 538 (1933).
56. Asahina, Acta Phytochimica, 2, 1 (1924).

groups in the furan series by means of bromine in the presence of direct sunlight, a similar oxidation under more strenuous conditions was attempted with the hope of obtaining a tri- or a tetracarboxylic acid. 44.8 g. (0.28 mole) of dry bromine was added dropwise with stirring over a period of three hours at 150-155° (bath temp.) to 24.9 g. (0.112 mole) of the ester contained in a 250 cc. Corex three-necked flask. A Corex mercury vapor arc lamp was operated at a distance of 25 cm. from the reaction flask. The bromine was completely absorbed at first, accompanied by vigorous evolution of hydrogen bromide. Following the addition of the bromine the mixture was stirred for thirty minutes longer at 150°, after which the excess bromine and occluded hydrogen bromide were swept out of the apparatus by means of a stream of dry carbon dioxide. The dark viscous oil was then refluxed for thirty minutes with 500 cc. of water. The ethereal extract of the chilled hydrolysate yielded a small amount of a crystalline acidic substance which melted at 185° after crystallization from ethanol. This product contained bromine.

Treatment of 2,5-Dimethyl-3,4-Furandicarboxylic Acid with Mercuric Acetate

Ortho-nitrophthalic acid upon treatment with mercuric acetate yields the corresponding nitroanhydro-hydroxymercuribenzoic acid, which is then treated with an aqueous solution of sodium bromide and bromine to form 2-bromo-3-nitrobenzoic

acid[57]. Following this procedure a solution of 15 g. (0.081 mole) of 2,5-dimethyl-3,4-furandicarboxylic acid in 64 cc. of water containing 6.4 g. (0.16 mole) of sodium hydroxide was added to a solution of 28.3 g. (0.089 mole) of mercuric acetate in 56 cc. of water and 4 cc. of glacial acetic acid. A heavy precipitate formed at once. The reaction mixture was slowly heated to 170° (bath temp.) and held at this temperature for eight hours. A feeble evolution of carbon dioxide occurred during this period. The brown solid was filtered out from the chilled reaction mixture and washed several times with water. The yield of dried product was 35 g. When this material was treated in the prescribed manner, the only product isolated was 2,5-dimethyl-3-furoic acid, which was evidently formed by decarboxylation during the initial heating.

57. Org. Syn., VII, 1, 12

II. Investigation of Some β-Furoic Acids[+]

Synthesis of 3-Furoic Acid

In the course of studies on orientation in the furan series it became evident that simple mono-β-substituted furans would lend themselves admirably toward a solution of this problem. One of the most important of these compounds was 3-furoic acid, since it not only would undergo nuclear substitution reactions with ease, but also would furnish a primary reference compound. A number of ring closure reactions were attempted in the preparation of this compound, only one of which was successful.

1. Reaction of Formylacetic Ester with Bromacetaldehyde

34.5 g. (0.25 mole) of sodium formylacetic ester was suspended in 200 cc. of absolute ether to which was then added dropwise with stirring 30.8 g. (0.25 mole) of bromacetaldehyde. The mixture was gently refluxed with stirring for four hours, at which point a copious precipitate of sodium bromide had formed. The solvent was removed from the filtrate under reduced pressure, leaving a dark brown oil, which still contained a small amount of bromacetaldehyde. The product was treated with an equal volume of fuming hydrochloric acid. After twenty minutes the mixture was steam distilled and the distillate

+ For additional information on this subject see Refs. 5, 17, 19, 54; Gilman, Burtner and Smith, J. Am. Chem. Soc., 55, 403 (1933) (58)
Gilman and Burtner, J. Am. Chem. Soc., 56, 0000 (1934) (59)

extracted with ether. The ether was removed under reduced pressure yielding an oily residue, which was then refluxed for one and one-half hours with alcoholic potassium hydroxide. Upon removal of the alcohol and careful acidification a brown acidic solid precipitated, which resisted all efforts toward crystallization and showed no melting point. When heated on platinum foil the material darkened, charred and finally burned off leaving no residue. A duplicate experiment yielded similar results.

2. Reaction of Formylacetic Ester and α,β-Dichloroethyl Ether

A solution of 48 g. of sodium hydroxide in 480 cc. of water was added rapidly with stirring at laboratory temperature to a solution of 50 g. (0.43 mole) of formylacetic ester and 85.8 g. (0.6 mole) of dichloroethyl ether. The reaction mixture was chilled immediately, extracted with ether and the extract dried over sodium sulfate. After removal of solvent the residual material was refluxed for three hours with 300 cc. of 10% alcoholic potassium hydroxide. After distilling off the alcohol and acidifying the residue, a pale yellow acidic substance precipitated, which was identified as trimesic acid, 1,3,5-benzenetricarboxylic acid.

3. Treatment of Sodium Formylacetic Ester with Iodine

In accordance with the formation and condensation of diethyl diacetosuccinate, 35 g. (0.24 mole) of the sodium salt suspended in ether was treated with an ethereal solution of iodine in small portions with shaking until the iodine was

no longer absorbed. The solid material was filtered out and the filtrate treated with sulfur dioxide to reduce free iodine. Subsequent to removal of the solvent the residual material was refluxed with approximately ten times its volume of 10% sulfuric acid for six hours. There was an insipid evolution of carbon dioxide. The reaction mixture was then subjected to steam distillation with no result. In the distillation flask there was formed an amorphous acidic substance, which showed no melting point when heated on platinum foil.

4. Treatment of Coumalic Acid with Aqueous Bromine

Aqueous bromine reacts smoothly with dimethylcoumalic acid to form 2,4-dimethyl-3-furoic acid[44]. In order to determine whether this reaction might be applied in the synthesis of 3-furoic acid, 14 g. (0.1 mole) of coumalic acid was treated with an equal weight of bromine in 100 cc. of water at laboratory temperature. Since no reaction took place when the temperature was raised to 70°, the reaction mixture was heated in a sealed tube at 120° for six hours. The only product obtained by this treatment was a small amount of bromocoumalic acid.

5. Decarboxylation of 2,4-Furandicarboxylic Acid

2,4-Furandicarboxylic acid prepared by the action of aqueous potassium hydroxide on methyl bromocoumalate[43] was decarboxylated to form 3-furoic acid in 80% yield[54, 60].

60. Reichstein and Zschokke, Helv. chim. acta., 15, 268 (1932).

5'-Bromo-2,2'-Furyl-3-Furoic Acid

This synthesis was carried out with the hope of obtaining α-bromodifuryl, which should form the corresponding RMgX compound to yield upon carbonation a difuryl derivative containing a carboxyl group in a position suitable as a resolving group in studies on difuryl isomerism.

109.5 g. (0.5 mole) of ethyl 5-bromo-2-furoate dissolved in 154 g. (1.75 mole) of ethyl acetate was added to 28.8 g. (1.25 mole) of sodium in the form of wire. After the initial violence had subsided, 22 g. of ethyl acetate was added and the reaction mixture warmed on a water bath until the sodium had reacted completely. Upon careful acidification with 10% hydrochloric acid a dark red oil formed, which was removed by extraction with ether. After the extract was dried over anhydrous sodium sulfate, the solvent was distilled off and the residium fractionated under reduced pressure, collecting the ethyl 5-bromo-2-furoylacetate boiling at 131-135°/3 mm. The yield was 44.5 g. or 34% of the theoretical. No analysis was made, but the structure of this compound was proven by hydrolysis to the known 5-bromo-2-furyl methyl ketone.

240 cc. of a 10% solution of sodium hydroxide was added rapidly with stirring to a solution of 52.2 g. (0.2 mole) of ethyl 5-bromo-2-furoylacetate and 40 g. (0.28 mole) of dichloroethyl ether at ordinary temperature. Stirring was continued for five minutes longer and the chilled reaction mixture extracted with ether. Subsequent to the removal of the solvent

there remained a yellow oil, which was distilled under diminished pressure. The 15 g. fraction distilling at 130-135°/17 mm. melted at 86° and was identified as 5-bromo-2-furyl methyl ketone by a mixed melting point determination. The distillation residue was refluxed with 0.15 mole of alcoholic potassium hydroxide for two hours. The alcohol was removed under reduced pressure and the residue carefully acidified to yield a dark amorphous solid, which after several crystallizations from hot water melted with decomposition at 166°. The product contained bromine but was obtained in an amount too small to warrant further investigation.

Attempted Synthesis of 5-Methyl-3-Furoic Acid

46.2 g. (0.5 mole) of chloroacetone was added dropwise with stirring at laboratory temperature to 69 g. (0.5 mole) of sodium formylacetic ester suspended in 300 cc. of dry ether. The mixture was refluxed with stirring for four hours and then filtered. Concentration of the filtrate yielded a white crystalline solid melting at 133°, which was identified as triethyl trimesate. 5-methyl-3-furoic acid has since been synthesized[58].

Synthesis of 2-Methyl-3-Furoic Acid

This reaction was carried out merely to show that bromacetaldehyde was capable of coupling with the sodium salts of acylacetic esters in an orthodox manner and, hence, could be used in ring closure reactions of this type. Sodium ethyl-

acetoacetate, prepared from 32.5 g. (0.25 mole) of ethyl acetoacetate, and 27 g. (0.22 mole) of bromacetaldehyde were condensed in the same manner as above. When worked up by the usual method a small amount of 2-methyl-3-furoic acid was obtained.

Attempted Nitration of 5-Nitro-2-Methyl-3-Furoic Acid

In an attempt to replace a β-carboxyl group by a nitro group 2 g. (0.011 mole) of 5-nitro-2-methyl-3-furoic acid[17] was added at 10° to the nitrating mixture prepared from 6 g. of fuming nitric acid and 6 g. of sulfuric acid. The reaction mixture was stirred for thirty minutes, poured onto 200 g. cracked ice and then extracted with ether. The ethereal extract was washed with 10% sodium carbonate and dried over sodium sulfate. No product was obtained when the ether was evaporated. The sodium carbonate wash solution was then acidified to yield 1 g. of unchanged 5-nitro-2-methyl-3-furoic acid.

3-Furyl-α-Naphthalide

Although Gilman and Wright[7] as well as Johnson[12] were unable to effect the formation of a 3-furylmagnesium halide from any of the β-halogenofurans, it was deemed advisable to prepare this naphthalide for identification purposes in the event that future attempts in this direction might be more successful.

2 g. of crude 3-furoyl chloride dissolved in 13 cc. of benzene was added in small portions with subsequent shaking

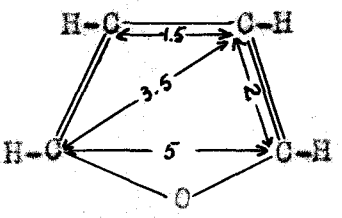
to a mixture of 2.5 g. of α-naphthylamine, 32 cc. of benzene and 10 cc. of 20% sodium hydroxide. The curdy white precipitate was filtered out, washed several times with dilute hydrochloric acid and recrystallized from ethanol to a constant melting point of 192°. The yield was approximately 1 g.

Anal. Calc'd. for $C_{18}H_{11}O_2N$: C, 75.95; H, 4.64
Found: C, 76.08; H, 4.47.

III. Study of Furandicarboxylic Acids

Observations made concerning the experimental conditions for substitution of the furandicarboxylic acids in that which follows lend added support to an hypothesis which may be applied to furan nuclear substitution reactions in general. Using the simple dibasic acids as an example let us make the following assumptions:

1. The carbon atoms as well as the oxygen atom lie in the same plane.
2. A two dimensional figure representing the furan nucleus is shown as below.



From the spatial relationships it may be seen that the distance between carbon atoms (2) and (5) is the greatest, between (3) and (5) the next greatest, etc., with that between (3) and (4) the least. From the laws of electrostatics it is known that like charges repel and unlike charges attract. Hence, if a negative group is to be introduced into an already negatively substituted nucleus, the more remote the position which can be assumed by the entering group from the negative group in place, the greater the ease of reaction. Conversely,

as this distance diminishes, the difficulty of substitution increases, thus demanding more strenuous conditions, such as elevated temperature, increased concentration etc., until finally the point is reached where substitution virtually becomes impossible due to breakdown of the reactants. Bearing in mind that α-substitution where possible is always preferential to β-substitution, let us examine the facts at our disposal concerning substitution of the simple furandicarboxylic acids.

In the case of 2,5-furandicarboxylic acid it is found that, in spite of numerous attempts in which a wide variety of conditions of temperature and pressure have been employed, no example of direct nuclear hydrogen substitution has been reported[+]. This fact is in accord with the theory, since any entering negative group must assume a position directly adjacent to a negative group already present. To effect such a reaction would require a definite amount of energy to bring the two negative groups together. Another opposing factor to such a substitution reaction lies in the fact that both α-positions are blocked. It is not at all unreasonable to suppose that the required amount of energy is of a greater magnitude than that available under conditions tolerable to nuclear furan substitution. If it were possible to introduce directly a positive group, such a reaction should go with relative ease, but, unfortunately, no definite case of direct substitution of such a nature is available in furan chemistry to date.

+ See reference (11) for a polychloraddition product.

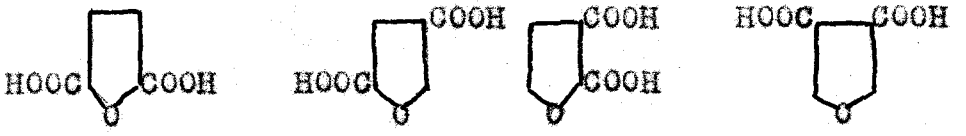
Considering next the 3,4-furandicarboxylic acid, we find practically the same spatial relationships concerning conditions for substitution, with the important exception that the α-positions are open. The latter fact should facilitate substitution to some extent, since it relieves one of the opposing forces encountered in the case of 2,5-furandicarboxylic acid. However, it is to be expected that the entrance of a negative group would proceed with great difficulty. Such indeed was found to be the case. In unpublished work by Willard Kirkpatrick as well as by the author a number of attempted nitrations were carried out using a wide range of severity of experimental conditions. Either no reaction occurred or the furan nucleus was ruptured by oxidation resulting in the formation of oxalic acid. In the case of helogenation, where more strenuous conditions may be employed without accompanying breakdown of the reactants, the dimethyl ester was found to undergo bromination in a sealed tube at 160° in the absence of a solvent.

A similar situation is encountered with 2,4-furandicarboxylic acid. The greatest distance between the negative group already present and the entering negative group is still of the same magnitude, according to the diagram. Likewise an α-position is vacant. Thus, it would be predicted that approximately the same possibility of substitution exists as with the 3,4-furandicarboxylic acid. Such has been found to be the case as regards halogenation, sulfonation and nitration.

Turning our attention now to 2,3-furandicarboxylic acid,

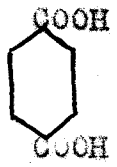
we find conditions for substitution more favorable. Here, the distance between the position assumed by the entering negative group and that already present in the nucleus is considerably greater than in the previously cited cases, namely 3.5 as compared to 2. On this basis substitution should proceed with far greater ease than with the other isomers. Again we find the facts in striking accord with the theory. Nitration was effected in 68% yield with ease in acetic anhydride at -15° to -10°. Likewise, the dimethyl ester underwent bromination readily in a relatively dilute chloroform solution at 15° to 20°. Temperature control by means of an ice bath was necessary in the latter case. Almost identical conditions for substitution were observed in the case of 4-methyl-2,3-furandicarboxylic acid[59], although it may be argued that the methyl group exerts a labilizing or activating influence in this example.

Another less direct source of evidence in favor of the proposed configuration of the furan nucleus is found in a comparison of the melting points of the several furandicarboxylic acids.

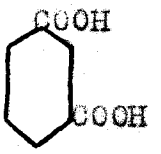


>350° 266° 221° 217°

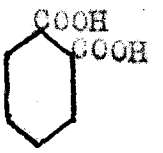
From these facts one may conclude that the greater the distance between the carboxyl groups, the higher the melting point. The same generalization applies to the phthalic acids.



>350°



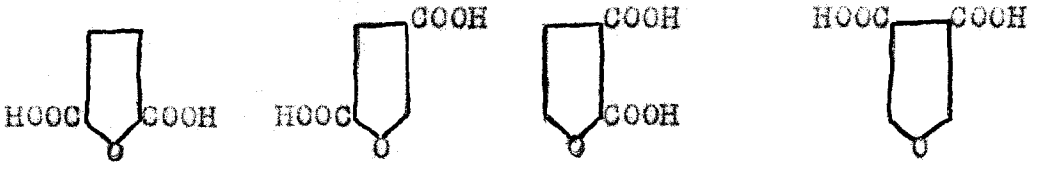
about 300°



184°

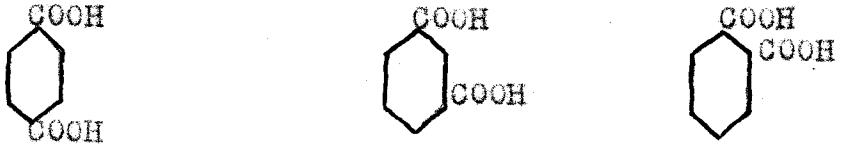
If there is any merit in this generality, then the distance between carbon atoms (2) and (4) in the furan nucleus could not be greater than that between (2) and (5), as is demanded by the structure commonly written.

Still another observation in the same direction is found in a comparison of water solubilities. When arranged in the order of increasing solubility, the furandicarboxylic acids appear as follows:



water solubility increases →

Again the analogy applies to the phthalic acids.



(solubilities in g./100 g. water at 25°C.)

Quantitative studies of anhydride formation and steric hindrance effects should shed considerable light on this situation.

Attempted Nitration of 2,4-Furandicarboxylic Acid

3.1 g. (0.02 mole) of the dry acid was added in portions with stirring at -10° to the nitrating mixture prepared from 7.3 g. (0.11 mole) of fuming nitric acid and 15.7 g. of acetic anhydride. After one hour the reaction mixture was poured upon 100 g. of cracked ice and filtered. The dried precipitate, which consisted of unreacted dibasic acid, weighed 2 g. Concentration of the filtrate yielded an additional 1 g. Check runs showed similar results.

3.1 g. (0.02 mole) of 2,4-furandicarboxylic acid was added in small portions with stirring to 15 g. of 20% fuming sulfuric acid at +10°. After one hour the reaction mixture was allowed to stand overnight at laboratory temperature. 15 g. of fuming nitric acid was then added slowly with stirring at 5-10° and the stirring continued for one hour longer. No product was isolated when the reaction mixture was poured onto ice and concentrated under reduced pressure.

Nitration of the dimethyl- and the monomethyl ester of 2,4-furandicarboxylic acid under the conditions previously described yielded equally discouraging results.

Attempted Bromination of 2,4-Furandicarboxylic Acid

12.0 g. (0.075 mole) of bromine was added dropwise with stirring to a solution of 7.8 g. (0.05 mole) of the dibasic acid in 20 cc. of glacial acetic acid at 5°. The temperature was allowed to rise to 15° and stirring continued for an

additional half hour. When worked up in the usual manner, practically a quantitative recovery of the original material was obtained. These results were checked by E. W. Smith, who later was able to brominate the dimethyl ester in a sealed tube at 160°[54].

A New Synthesis of 4-Methyl-5-Furoic Acid

It was hoped that this method might be one which would require fewer steps and a less involved procedure than that of Reichstein[24]. However, the over all yield of methyl furoic acid was insufficient to warrant the use of this synthesis as a method of preparation. The following sequence of reactions was carried out: 3,4-furandicarboxylic acid → 5-carbomethoxy-4-furoic acid → 5-carbomethoxy-4-furoyl chloride → 5-carbomethoxy-4-furaldehyde → 5-carboxy-4-furaldehyde → 5-carboxy-4-furaldehyde hydrazone → 4-methyl-5-furoic acid.

16 g. (0.1 mole) of 3,4-furandicarboxylic acid, 45 g. (1.4 mole) of methyl alcohol and 30 g. of concentrated sulfuric acid were heated with stirring at 100° (bath temp.) for one hour. The mixture was then poured upon 100 g. of cracked ice and worked up in the customary manner to yield 17.5 g. of the crude monomethyl ester, which after crystallization from methanol melted at 122°.

17 g. (0.1 mole) of 5-carbomethoxy-4-furoic acid and 23.8 g. (0.2 mole) of thionyl chloride were gently refluxed for nine hours. After removal of the excess thionyl chloride,

the residue was distilled under reduced pressure, collecting the product boiling at 115-118°/2 mm. The yield was 11.9 g. or 70% of the theoretical.

5 g. of the above acid chloride, 2 g. of palladium-barium sulfate catalyst and 25 cc. of xylene were used in this reduction. At the end of three hours the reaction was complete, and after removal of the xylene there remained 4-5 cc. of a dark oil, which was hydrolyzed directly to the acid by means of 6 N hydrochloric acid. The ethereal extract of the chilled hydrolysate was dried and the solvent distilled off, leaving 3 g. of a yellow crystalline solid, which after crystallization from water melted at 197° with decomposition. This product gave a positive Schiff's test but no aniline acetate color reaction.

5.5 g. (0.04 mole) of the aldehyde acid in 15 cc. of methanol was treated with 5 g. (0.1 mole) of hydrazine hydrate at -15°. After standing for one and one-half hours, the mixture was warmed in a water bath to 75° for a few minutes, then chilled and filtered. The air dried product weighed 3.5 g. After crystallization from water the product was a pale yellow microcrystalline powder melting at 205° with decomposition.

The 3-carboxy-4-furaldehyde hydrazone was heated with potassium hydroxide to give a small amount of an acid, which after several vacuum sublimations melted at 138°. A mixed melting point with an authentic specimen of 4-methyl-3-furoic acid prepared by Reichstein's method showed no depression.

It should be mentioned at this point that M. R. McCorkle

and the author have found it unnecessary to separate the ethyl 4-methyl-5-carboethoxy-2-furylacetate from the corresponding pyrrol derivative by the tedious process of steam distillation, as reported by Reichstein in his synthesis of 4-methyl-5-furoic acid. An efficient separation of this mixture may be effected by one fractionation under reduced pressure. The latter method not only simplifies the manipulation, but also increases the yield about 15%

Decarboxylation of 2,4-Furandicarboxylic Acid

In addition to the method previously cited[54], the decarboxylation of this compound has been effected in several other ways.

First, 4.85 g. (0.025 mole) of monopotassium 2,4-furandicarboxylate was heated in a sealed tube at 280° for three hours. Since on opening the tube no gas evolution was noticeable, the contents were transferred to a large test tube and heated to approximately 400° in a metal bath, at which temperature carbon dioxide was liberated. Heating was continued until gas evolution had ceased. About 0.5 g. of 5-furoic acid was removed from the upper part of the tube. The residue upon acidification yielded a small amount of the original dibasic acid.

1.5 g. of the monomethyl ester of 2,4-furandicarboxylic acid, 5 g. of quinoline and 1 g. of copper-bronze were heated in a sidearmed-test tube at 180° in a metal bath, at which point evolution of carbon dioxide began. The temperature was gradually

raised to 190-195° and held there until gas evolution was complete. A few drops of a light yellow oil had collected in the receiver during this period. The quinoline was then distilled over and the chilled distillate carefully acidified with 10% hydrochloric acid. Upon removal of the solvent from the dried ethereal extract, there remained a small quantity of a fragrant yellow oil, which was gently refluxed with 5 cc. of 25% alcoholic potassium hydroxide for two hours. The alcohol was distilled off and the residue acidified to yield 0.15 g. of 3-furoic acid melting at 120°. This experiment also proved that half-saponification of the esters of α, β-furandicarboxylic acids affects only the -COOR group in the α-position.

According to the directions of Gilman and Wright[7], 20 g. (0.11 mole) of 2,4-furandicarboxylic acid and 29.8 g. (0.11 mole) of mercuric chloride in 80 cc. of water were refluxed for one hour, accompanied by a feeble evolution of carbon dioxide. 44 cc. of 10% sodium hydroxide (0.11 mole) was added and heating continued. This treatment greatly increased the rate of decarboxylation. After four hours gas evolution had ceased, whereupon the chilled reaction mixture was filtered. The filtrate was then acidified, saturated with hydrogen sulfide, heated to boiling and filtered. The ethereal extract of the chilled filtrate contained 4 g. (52.4%) of 3-furoic acid melting at 120°.

5-Iodo-3-Furoic Acid

15.6 g. (0.1 mole) of 2,4-furandicarboxylic acid was converted

to the disodium salt and heated in a steam autoclave at 150° for one hour with 50.8 g. (0.2 mole) of iodine, 90 g. of potassium iodide and 200 cc. of water.[61, 62] After standing for twelve hours the unreacted iodine was reduced with sulfur dioxide, whereupon a yellow crystalline acid precipitated, melting at 164°. Crystallization from 20% acetic acid produced a pure white product, M.P. 167.5°. The yield was 5.2 g. or 24% of the theoretical.

Anal. Calc'd. for $C_5H_3O_3I$: I, 53.36. Found: I, 53.18

3 g. of 5-iodo-3-furoic acid, 6 g. of zinc dust, 10.5 g. of ammonium chloride and 30 g. of water were gently refluxed for twelve hours. The reaction mixture was worked up in the usual manner to yield 1.2 g. (85%) of 3-furoic acid melting at 122°. A mixed melting point determination with an authentic sample gave no depression.

Attempted Preparation of 3-Iodo-4-Furoic Acid

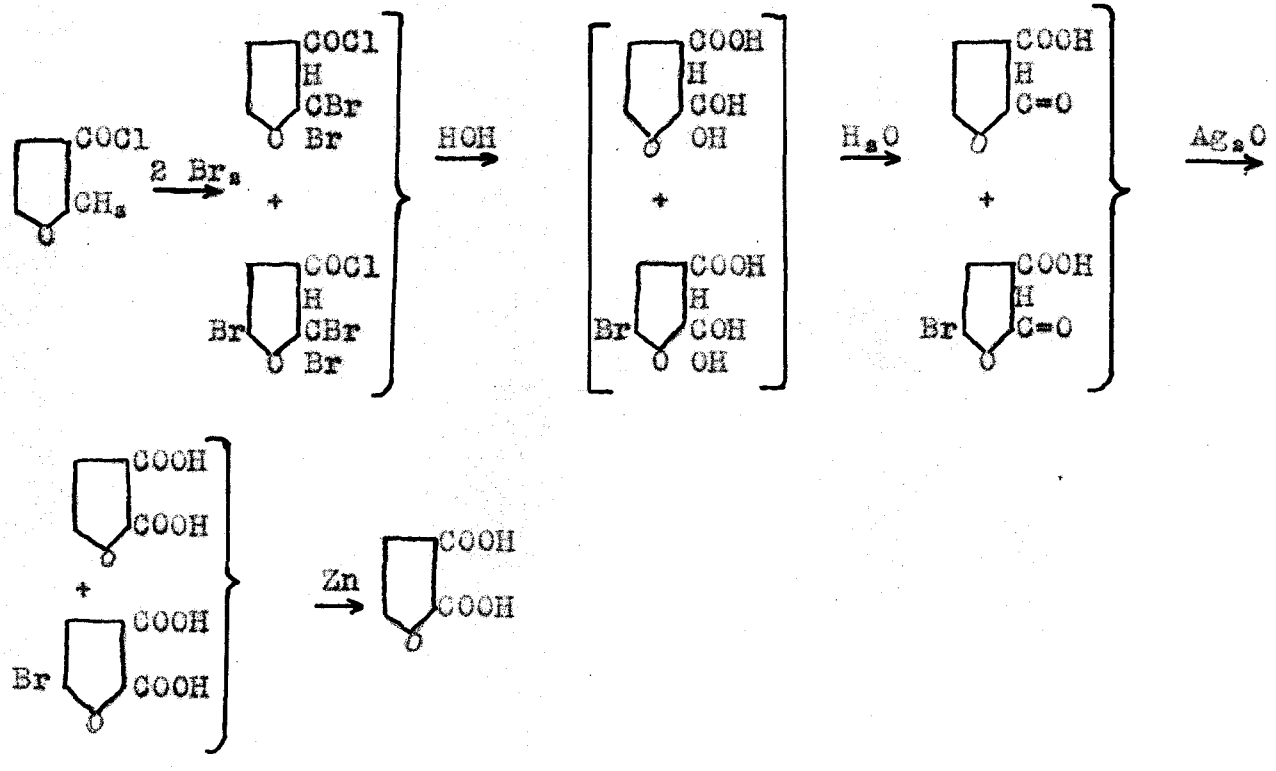
In the same manner 16.1 g. (0.11 mole) of 3,4-furandicarboxylic acid was converted to the disodium salt and autoclaved with 56 g. (0.22 mole) of iodine, 75 g. of potassium iodide and 200 cc. of water. The iodine was reduced as before and the precipitated material crystallized from water to yield 12.5 g. of the unchanged dibasic acid melting at 214°.

61. Phelps and Hale, Am. Chem. J., 25, 445 (1901)
62. Gilman, Mallory and Wright, J. Am. Chem. Soc., 54, 733 (1932).

2,5-furandicarboxylic acid readily undergoes replacement of the carboxyl groups by iodine. 2,4-furandicarboxylic acid likewise yields its ∝-carboxyl group to replacement. However, the 3,4-furandicarboxylic acid and the 2,5-dimethyl-3-furoic acid do not undergo this reaction. The latter case may be considered as a critical test, since the methyl groups tend to activate other substituents within the molecule. Therefore, it may be concluded that this replacement is specific for ∝-carboxyl groups only.

Improved Directions for the Preparation of 2,3-Furandicarboxylic Acid

Asahina[56] has reported the preparation of this compound by the oxidation of 2-methyl-3-furoyl chloride by means of bromine in the presence of direct sunlight. The net yield of 2,3-furandicarboxylic acid in this case was 15.3%. The course of reaction is evidently as follows:



The improved directions involve the same proportions of starting materials, using a Corex mercury vapor arc lamp as a source of illumination instead of direct sunlight. In this manner 40 g. (0.25 mole) of dry bromine was added dropwise with stirring at 130-135° (bath temp.) over a period of four hours to 19 g. (0.13 mole) of 2-methyl-3-furoyl chloride contained in a 250 cc. Corex three-necked flask fitted with an efficient condenser. After hydrolysis and oxidation by means of silver oxide in the prescribed manner, there was obtained 20 g. of the mixed acids.

Reduction by means of zinc dust and dilute ammonium hydroxide rather than ammonium chloride was found to be more reliable. Accordingly, 20 g. of the mixed acids was treated separately in 5 g. portions with an equal weight on zinc dust and 100 g. of ammonium hydroxide (sp. g., 0.975). It was necessary to add more ammonium hydroxide from time to time in order to keep the reaction mixture strongly ammoniacal. After being refluxed with stirring for eight hours, the mixture was filtered hot and the solvent removed from the ether extract of the chilled filtrate to yield 8 g. of the 2,3-furandicarboxylic acid melting at 218°. Crystallization from glacial acetic acid yielded a pale yellow product melting at 220-221°, which showed no depression in melting point when mixed with an authentic specimen kindly furnished by Asahina. The net yield was 40% based on the moles of 2-methyl-3-furoyl chloride used to start with.

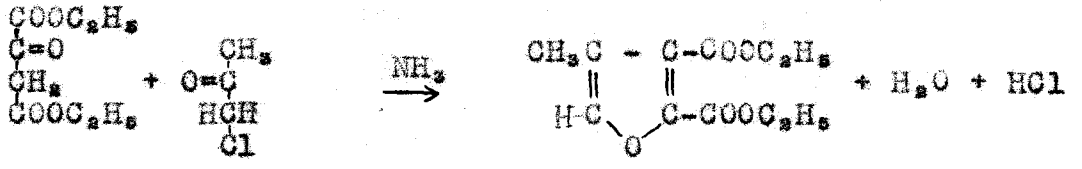
Oxidation of 2,4-Dimethyl-3-Furoic Acid

Using the method of W. A. Noyes[63], 2 g. of 2,4-dimethyl-3-furoic acid, 50 g. of potassium ferricyanide, 20 g. of potassium hydroxide and 300 g. of water were refluxed for three hours in an efficient hood. The chilled mixture was filtered, acidified, refiltered and extracted thoroughly with ether. After removal of solvent there remained a small amount of an acidic solid, which was subjected to steam distillation to remove the unchanged dimethyl furoic acid. Ether extraction of the steam distillation residue produced a gummy material, which upon crystallization from a benzene-ether mixture melted at 248-250°. Sublimation under diminished pressure followed by crystallization from acetic acid gave a white product melting at 274° with decomposition. When mixed with an authentic specimen of Sutter's 2,3,4-furantricarboxylic acid[30], no depression in melting point was observed. The identity of this compound was further established by a mixed melting point determination with the trimethyl esters of these two acids as well as with that prepared by Reichstein[31] by decarboxylation of furantetracarboxylic acid. Studies now in progress by E. V. Brown have shown this method of oxidation to be applicable to a large variety of alkyl-substituted furan derivatives.

Attempted Ring Closure Synthesis of 4-Methyl-2,3-Furandicarboxylic Acid

63. W. A. Noyes, Am. Chem. J., 5, 97 (1883).

This compound, as a source of 4-methyl-3-furoic acid, has come into demand recently in this laboratory. Reichstein[24] has described its synthesis, although a rather tedious series of reactions was involved. It was hoped that the method of Feist[64], used in the preparation of dimethylpyrrolcarboxylic acids, might be so modified as to produce the desired furandicarboxylic acid.



A solution of 31 g. (0.16 mole) of oxalaceticester and 16 g. (0.16 mole) of chloroacetone in 600 cc. of dry ether was saturated with gaseous ammonia at 0° over the course of one hour. The pasty mixture was then allowed to stand at laboratory temperature for one hour, whereupon the solvent was distilled off and the residue warmed on a water bath at 70° for fifteen minutes. The residue was taken up with 300 cc. of water, ether extracted, and the extract washed with 5% sodium hydroxide until the washings were no longer colored. After being washed thrice with 5% hydrochloric acid and thence with water, the ethereal solution was dried and the solvent removed, leaving a dark oil. Refluxing with alcoholic potassium hydroxide yielded none of the expected furandibasic acid.

64. Feist, Ber., 35, 1552 (1902).

Attempted Preparation of 2,4-Dimethyl-3,5-Furandicarboxylic Acid

17.6 g. (0.064 mole) of ethylbromocoumalate was shaken with a solution of 19.6 g. (0.35 mole) of potassium hydroxide in 39 cc. of water. The ester dissolved and the reaction mixture darkened with very little heat effect. The solution was refluxed for thirty minutes, chilled and carefully acidified with a solution of 17.1 g. of sulfuric acid and 16 g. of water. After evaporation to dryness on a steam plate, the dark gummy residue was extracted for six hours with 300 cc. of acetone in a Soxhlet apparatus. The acetone was then distilled off and the residue crystallized from water yielding a gummy yellow substance, which was taken up in dilute alkali, washed with ether, acidified and ether extracted. Upon removal of solvent from the ether extract, there remained 5.1 g. of a light yellow crystalline acid, which after repeated crystallization from water melted at 194°. This material showed acidic properties and contained no halogen. The neutralization equivalent was 73.3 as compared with a calculated value of 92.

Anal. Calc'd. for $C_8H_8O_5$: C, 52.16; H, 4.34. Found: C, 50.07; H, 4.67.

Decarboxylation did not yield the expected 2,4-dimethyl-3-furoic acid; instead, a colorless neutral liquid was obtained which has not been identified.

SUMMARY

The methods of synthesis of β-substituted furans have been reviewed. A number of reactions have been effected, first, in order to determine the structures of some of these compounds; second, to provide a series of reference compounds which will facilitate orientation studies; and, third, to gain a more thorough understanding of nuclear substitution reactions in the furan series.